BG01859

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 430 491 A2

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 90312435.2

(22) Date of filing: 14.11.90

(51) Int. Cl.5: A61L 15/16, A61K 9/70, A61M 37/00

(30) Priority: 17.11.89 AR 315479

(43) Date of publication of application: 05.06.91 Bulletin 91/23

(84) Designated Contracting States: AT BE CH DE DK ES FR GB GR IT LI LU NL SE Bulletin

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(54) Transdermal delivery device for estradiol and process for manufacturing said device.

(57) A transdermal delivery device for estradiol comprises a flexible substrate and a releasable protective film. The protected surface of the flexible substrate is at least partly covered with a coating layer containing (a) a dermatologically acceptable pressure sensitve adhesive material for securing the device to the skin, (b) estradiol homogeneously distributed as a pharmacologically active ingredient and (c) a component which enhances the rate of estradiol permeation and which comprises from 1 to 20 wt% of at least one first compound selected from unsaturated (C_{12}-C18) fatty acids and alkyl esters thereof, and from 5 to 30 wt% of at least one second compound selected from glycerin and (C_3-C_6)alkylene 1,2-diols, the percentages being based on the total weight of said coating layer.
A process for manufacturing such a device is also decribed.

EP 0 430 491 A2

TRANSDERMAL DELIVERY DEVICE FOR ESTRADIOL AND PROCESS FOR MANUFACTURING SAID DEVICE

The present invention relates to a device or system (hereinafter "device") for the administration of estradiol by the transdermal or percutaneous route, and to a process for manufacturing said device.

BACKGROUND OF THE INVENTION

The transdermal or percutaneous administration of drugs provides a new and useful alternative to classical methods, and has been developed since 1980 (R.W. Baker and J. Farrant "Patents in transdermal drug delivery", Drug Delivery Systems 1987 Conference Proceedings) for the systematic treatment of various medical conditions to provide constant and efficient levels of nitroglycerin in the blood (USSN 806257 filed 6th November 1985, USSN 275215 filed 18th April 1985/85 and U.S. Patent No. 3996934); and also to administer various types of steroids, such as ethynyl estradiol (EPA 0279282), estradiol (USSN 806257), and various anti-inflammatories (EPA 0287817), for example.

All known devices have in common a bandage or flexible substrate, a protective release film and a layer in which the active ingredient is dispersed in a vehicle which, in certain cases, contains adhesive components ("adhesive device") and in other cases an adhesive material is provided in an external layer and the active ingredient is contained in a separate layer or intermediate matrix (these devices are called respectively "monolithic devices" and "reservoir devices", see R.W. Baker et. al, supra).

With the devices proposed and developed in the prior art, adjuvants known as "increasers", "enhancers" or "permeation enhancers" are also included for increasing the rate of permeation of the active ingredient. In addition to dimethylsulfoxide and azone (1-dodecylhexahydro-2H-azepin-2-one) (EP-A-0251245), ethanol, propylene glycols, other alcohols, long-chained fatty acids (and esters thereof) etc., have been also proposed (R.W. Baker et al, supra).

It has now been found that a further transdermal delivery device for estradiol can be obtained and is suitable for the treatment of side effects and menopausal disorders such as hot flushes, depression, osteoporosis, having rapid and sustained effects depending on the use of a binary "enhancer" component including a combination of at least one compound selected from unsaturated fatty acids (C_{12}-C_{18}) and alkyl esters thereof with at least one compound selected from glycerin and (C_2-C_4)alkylene-1,2-glycols.

It is an object of the present invention to provide a transdermal delivery device for the transdermal administration of estradiol (SAT) which allows a high transdermal flux with which it is possible to maintain estradiol at the required constant high level in the blood.

This invention further relates to a transdermal delivery device for estradiol whereby metabolic degradation of estradiol to estrone during permeation is inhibited to a large extent.

In one aspect, the present invention provides a transdermal delivery device for estradiol comprising a flexible substrate and a releasable protective film, the protected surface of said flexible substrate being at least partly covered with a coating layer containing (a) a dermatologically acceptable pressure sensitive adhesive material for securing the device to the skin, (b) estradiol homogeneously distributed as a pharmacologically active ingredient and (c) a component which enhances the rate of estradiol permeation and which comprises from 1 to 20 wt% of at least one first compound selected from unsaturated (C_{12}-C18) fatty acids and alkyl esters thereof, and from 5 to 30 wt% of at least one second compound selected from glycerin and (C_3-C_6)alkylene 1,2-diols, the percentages being based on the total weight of said coating layer.

The estradiol is preferably present in an amount exceeding its saturation concentration in said coating layer.

In another aspect, the present invention provides a process for manufacturing the transdermal delivery device for estradiol, comprising the steps of providing a coating layer on at least part of one surface of a flexible substrate, said coating layer containing (a) a dermatologically acceptable pressure sensitive adhesive material for securing the device to the epidermis, (b) estradiol homogeneously distributed as a pharmacologically active ingredient and (c) a component which enhances the rate of estradiol permeation and which comprises from 1 to 20 wt% of at least one first compound selected from unsaturated (C_{12}-C18) fatty acids and alkyl esters thereof, and from 5 to 30 wt% of at least one second compound selected from glycerin and (C_3-C_6)alkylene 1,2-diols, the percentages being based on the total weight of said coating layer; and providing a releasable protective layer which, in the finished device, lies on the opposite side of the coating layer to the flexible substrate.

Preferably, the amount of estradiol in said coating layer is in excess of the saturation concentration therein.

Conveniently, the coating layer is provided by coating it on the releasable protective layer, eg a silicone layer, bringing the flexible substrate into contact with the coating layer, and then cutting the resultant structure to the required shape and size.

The releasable protective layer is discarded immediately before the device is applied to the skin of a patient. Obviously, the formulation of the coating layer, particularly the adhesive material, is not only dermatologically acceptable but also pharmacologically acceptable.

I) The adhesive material may be selected from a wide variety of pressure-sensitive adhesive materials such as silicones, rubber, PIB (polyisobutylene) and acrylic adhesives.

II) A reinforcing component (solid) which may be selected from the polyterpene resins, such as Piccolyte S115 (a terpene resin), Wingtack 115, modified colophony resins such as Pentalyn (an esterified colophony resin with pentaerythritol), etc. may also be included.

Amongst materials suitable for the flexible substrate, cellophane (cellulose xanthate film), Saran (polyvinylidene chloride film), polyvinyl chloride coatings, polyesters such as polyethylene terephthalate including binary structures such as aluminium-polyethylene coatings, polyester-polyethylene coatings, etc, may be used.

For the releasable protective layer, any of the above-mentioned coatings for the substrate can be used, preferably polyesters, such as polyethylene terephthalate, etc covered with a silicone to prevent sticking of the adhesive.

An amount of estradiol in the adhesive matrix of from about 1 to 5 per cent, preferably 2 per cent, by weight based on the total weight of the coating layeradhesive matrix, is sufficient for the purposes of this invention. The amount of estradiol preferably exceeds the saturation concentration thereof in said coating layer in order to keep the flux at a constant rate and thereby maintain a more constant level of estradiol in the blood. Indeed, it is possible to formulate coating layers without reaching saturation levels if the required dosage and the estradiol level so requires it.

The estradiol permeation enhancing component performs a vital role in the maintenance of constant systemic levels of estradiol.

The above mentioned alkylene diols and, particularly propylene glycol, have been proved to be an inhibitor of the skin metabolism degradation of estradiol to estrone, that is to say, the skin not only has a passive role recognized as protector against the penetration of exogenous agents, since it has been demonstrated as being a metabolizer of certain substances, among them estradiol which undergoes enzymatic degradation to estrone.

Tests conducted by the applicant have shown that propyleneglycol inhibits the enzymatic mechanism that causes the degradation of estradiol to estrone. Therefore, the propyleneglycol added (and other low chain alkylenediols) complements the enhancer effect of the fatty acids by avoiding or reducing estradiol degradation, thereby enabling systemic estradiol levels to be obtained which are higher than those obtainable by conventional transdermal delivery devices which operate without blocking said enzymatic mechanism, but which use, for example, oleic acid as "enhancer", as will be appreciated from Table 4 hereinafter.

The present invention will be further described in the following Examples

EXAMPLE 1

Preparation of formulas containing estradiol.

A) Preparation of an adhesive mixture.

To a vinyl acetate/acrylate polymer solution diluted with ethanol/toluene/ethyl acetate to 30% solids, a solid rosin tackifier component (Pentalyn A) is added with stirring at room temperature for a period of time necessary to obtain a homogeneous mixture (for about 4 hours)

B) Preparation of formula containing estradiol.

To the material prepared in step A) above, whilst stirring, estradiol and the permeation rate enhancer (a mixture of oleic acid and propylene glycol) are added. A clear solution is obtained and kept in a closed vessel to avoid evaporation of the solvent medium until air bubbles have dispersed. Finally, the solution is filtered through a stainless sieve (100 mesh).

C) Preparation of the transdermal delivery device.

On a flexible laminate (which later defines the releasable protective layer), the solution prepared as

described above, is applied by means of a conventional coating device. Said solution is applied to one of the surfaces of the flexible laminate (which may, for example, be a polyester film previously sprayed with silicone) to form a layer of predetermined thickness, for example, 400 micrometres, and is subsequent dried by hot air circulation.

The thus-coated siliconised polyester is laminated on a second flexible film which constitutes the substrate in the finished device.

The process ends with cutting to size, for example, by means die cutting of the multi-layer laminate to form shapes of the desired geometry and size.

TRANSDERMAL PERMEABILITY AND ESTRADIOL BIOAVAILABILITY OF TRANSDERMAL ADMINISTRATION ESTRADIOL

The rate of estradiol permeation in the formulations according to the present invention, was examined "in vivo" by measuring the estradiol blood level in 6 voluntary post-menopausal women, using devices of different surfaces as described in Example 1, estradiol concentration being measured in the blood plasma 24 hours after application.

The Table 1 below illustrates the result obtained

TABLE 1

Device surface (cm^2)	Estradiol level in plasma (pg/ml)
8.5	20.5 ± 2.4
17	50.5 ± 9.1
35	121.8 ± 37.2
	(mean values ± SEM)

The experiment was repeated with the device of Example 1 cut to $17cm^2$ to verify the amount of estradiol accumulated in the blood plasma, in assays lasting 72 hours.

TABLE 2

Time	Estradiol level (pg/ml)
24 hours	50.50 ± 9.11
48 hours	62.75 ± 11.78
72 hours	48.34 ± 6.55
	(mean values ± SEM)

Furthermore, "in vitro" permeation experiments with abdominal mouse skin and human skin were made using the diffusion chamber that is schematically shown in longitudinal section in Fig. 1.

The diffusion chamber illustrated in Fig. 1 comprises a body having front and rear tubular sections 1 and 2 having respective annular end flanges 3 and 4 by which the sections 1 and 2 are joined together. A sample of skin 5, with attached estradiol delivery device D to be tested facing the rear tubular section 2, is clamped between the flanges 3 and 4 by means of a pinch clamp 6.

The tubular section 1 has an internal chamber 7 with an opening 8 furnished with a glass stopper 9. The tubular section 1 also has a jacket 10 through which warm water can be circulated to maintain the contents of the chamber 7 at the desired temperature. The chamber 7 contains a magnetic bar stirrer 11 which is rotatable by means of a magnetic field applied by external means (not shown) to enable the contents of the chamber 7 to be stirred.

The tubular section 2 has a chamber 12 with an opening 13 furnished with a glass stopper 14.

In the assay, the skin of Swiss mice, shaved 72 hours before the experiments, was employed. Also used was human stratum corneum obtained from human skin samples (remnants of plastic surgery) which

had been treated by immersion in water at 60° C for a minute in order to separate the strateum corneum therefrom by exfoliation.

Both the hairless mouse skin and the human stratum corneum with estradiol delivery device attached were clamped between the flanges 3 and 4, as shown in Fig. 1, with the dermis towards chamber 12 which is a receptor chamber. Each experiment was started by loading chamber 7 with 5.5 ml of a receptor solution of sodium laurylsulfate (0.5 %), starting the stirrer 11 and taking samples at pre-determined periods of time and the subsequent determination of permeated estradiol (by HPLC).

The following illustrates the results obtained in assays performed under the above mentioned conditions using devices as described in Example 1.

TABLE 3

	Flux (µg/cm²/hour)			Accumulated Estradiol Permeation (µg/cm²)		
	5 h	24 h	48 h	5 h	24 h	48 h
Mouse skin	1.28	1.07	2.58	6.39	26.59	57.88
Human Strateum Corneum	0.24	0.84	0.88	1.18	13.94	48.91

The inhibition of the mechanism of the enzymatic degradation from estradiol to estrone to propyleneglycol has been studied using the same device as illustrated in Fig.1 as follows:

INHIBITION OF THE ESTRADIOL METABOLISM IN HUMAN SKIN

Strateum corneum was eliminated by scraping with a surgical knife at 37° C
CONTROL: Saturated solution of estradiol in saline solution.
PPG: Saturated solution of estradiol in saline solution + 10% PPG.
The results of two sets of experiments are shown (n=3 each).

TABLE 4

	Estradiol (nmol/ml)	Estrone (nmol/ml)	%Estradiol metabolized (E_1.100//E_2 + E_1)	%Inhib
Exp. 1				
Control	2.62	0.73	21.8	66.0
PPG	3.51	0.27	7.4	
Exp. 2				
Control	2.94	0.53	15.3	57.2
PPG	2.71	0.19	6.55	

This shows estradiol metabolism in human skin. Under the control conditions the metabolite, estrone, was between 21.8 and 15.3% of the estradiol present in the incubation bath, while with PPG 10% the conversion was inhibited by 57 - 63%. In mouse skin, the controls resulted in a change of 7-15% suffering an inhibition to 1-2% with PPG.

Claims

1. A transdermal delivery device for estradiol comprising a flexible substrate and a releasable protective film, the protected surface of said flexible substrate being at least partly covered with a coating layer

containing (a) a dermatologically acceptable pressure sensitive adhesive material for securing the device to the skin, (b) estradiol homogeneously distributed as a pharmacologically active ingredient and (c) a component which enhances the rate of estradiol permeation and which comprises from 1 to 20 wt% of at least one first compound selected from unsaturated (C_{12}-C18) fatty acids and alkyl esters thereof, and from 5 to 30 wt% of at least one second compound selected from glycerin and (C_3-C_6)alkylene 1,2-diols, the percentages being based on the total weight of said coating layer.

2. A device according to claim 1, wherein the amount of estradiol in the coating layer exceeds the saturation concentration thereof.

3. A device according to claim 1 or 2, wherein said coating layer comprises in an homogeneous mixture:

i) a polymer vehicle selected from silicones, acrylic or methacrylic polymers, natural or synthetic rubber and mixtures thereof;

ii) an adhesive material selected from polyterpenes, modified colophony resins and mixtures thereof.

4. A device according to claim 1, 2 or 3, wherein said component comprises oleic acid and propyleneglycol in a ratio of 1:0.5 to 1:5.

5. A device according to claim 4, wherein the ratio is 1:1.5.

6. A device according to any preceding claim, wherein said flexible substrate is of cellulose xanthate, aluminium, a polymer or a laminate of any two or more thereof.

7. A device according to claim 6, wherein the polymer is a polyvinyl chloride, polyvinylidene or polyethylene.

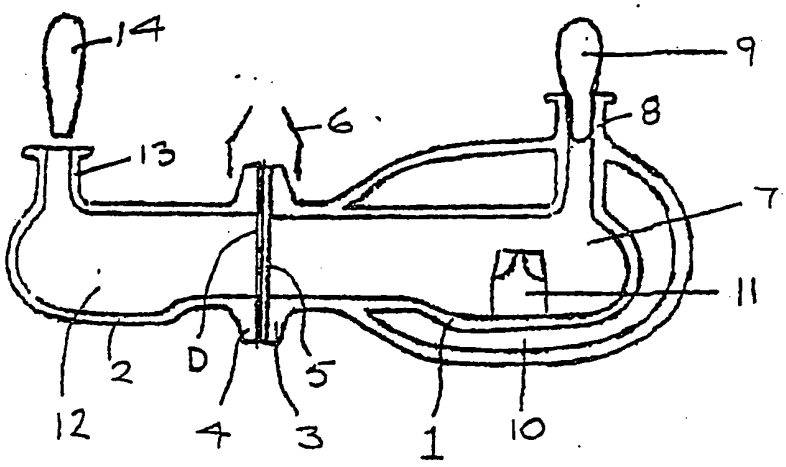
8. A device according to any preceding claim, wherein the amount of estradiol in the coating layer is sufficient to maintain its concentration at least at saturation level during predetermined periods of time.

9. A process for manufacturing a transdermal delivery device for estradiol, comprising the steps of providing a coating layer on at least part of one surface of a flexible substrate, said coating layer containing (a) a dermatologically acceptable pressure sensitive adhesive material for securing the device to the epidermis, (b) estradiol homogeneously distributed as a pharmacologically active ingredient and (c) a component which enhances the rate of estradiol permeation and which comprises from 1 to 20 wt% of at least one first compound selected from unsaturated (C_{12}-C18) fatty acids and alkyl esters thereof, and from 5 to 30 wt% of at least one second compound selected from glycerin and (C_3-C_6)alkylene 1,2-diols, the percentages being based on the total weight of said coating layer; and providing a releasable protective layer which, in the finished device, lies on the opposite side of the coating layer to the flexible substrate.

10. A process according to claim 9, wherein the amount of estradiol in said coating layer is in excess of the saturation concentration therein.

11. A process according to claim 9 or 10, wherein the coating layer is provided by coating it on the releasable protective layer, bringing the flexible substrate into contact with the coating layer, and then cutting the resultant structure to the required shape and size.

Fig.1



(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 430 491 A3

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: 90312435.2

(51) Int. Cl.5: A61L 15/16

(22) Date of filing: 14.11.90

(30) Priority: 17.11.89 AR 315479

(43) Date of publication of application:
05.06.91 Bulletin 91/23

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(88) Date of deferred publication of the search report:
27.12.91 Bulletin 91/52

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EP 0 430 491 A3

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 31 2435

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	WO-A-8 703 490 (KEY PHARMACEUTCALS, INC.)June 1987 * claims 1,2,8 * *	1	A 61 L 15/16
X	BIOLOGICAL ABSTRACTS, vol 88, nr 1, 1989, ab- stract nr 9062, Philadelphia, PA, US; GOODMAN et al.: "Action of penetration enhancers on skin as assessed by the permeation of model drug 5-fluorouracil and estradiol", & J. INVEST. DARMATOL. 91(4): 323-327. 1988 * abstract * *	1,4	
X,P	WO-A-9 008 120 (SCHERING CORPORATION)1990	1	
A,P	WO-A-9 008 120 (* page 4, line 4 - page 8, line 15 *)	2-11	
A	EP-A-0 171 742 (E.I. DU PONT DE NEMOURS AND COMPANY) 19 February 1986 * abstract * * * page 12, line 27 - line 34 * *	1-11	
A	EP-A-0 261 429 (WARNER-LAMBERT COMPANY)1988 * page 3, line 25 - line 57 * *	1-11	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			A 61 L

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	30 October 91	LEHERTE C.F.M.

CATEGORY OF CITED DOCUMENTS

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